Risk factors for symptoms of infection and microbial carriage among French medical students abroad

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Abstract

Objectives: To investigate symptoms of infections and their risk factors among French medical students undertaking an internship abroad.

Methods: Clinical follow up and qPCR-based respiratory, gastrointestinal, and vaginal pathogen carriage were prospectively assessed pre-travel and post-travel, in a cohort of medical students departing from Marseille, France.

Results: 293 students were included. 63.5%, 35.8% and 3.6% of students reported gastrointestinal, respiratory, and vaginal symptoms, respectively. The acquisition rate of Enteroaggregative *Escherichia coli* and Enteropathogenic *E. coli* was 40.9% and 18.6%, respectively. A significant increase was observed for rhinovirus and *Streptococcus pneumoniae* by comparing the prevalence of pathogens in pre-travel and post-travel samples. *Gardnerella vaginalis* and *Atopobium vaginae* acquisition rates were 12.9% and 13.9%, respectively. Being female, primarily travelling to Vietnam, and living in basic accommodation conditions were independent risk factors for reporting respiratory symptoms. Students reporting respiratory symptoms were three times more likely to acquire *S. pneumoniae*. Travelling primarily to north India and Senegal were independent risk factors for diarrhoea.

Conclusion: This study makes it possible to identify the main infectious diseases linked to travel in a group of French medical students undertaking an internship abroad and the risk factors on which to base targeting students for reinforced pre-travel advice.

Keywords*: respiratory symptoms, travellers' diarrhoea, medical students, Streptococcus pneumoniae, E. coli, risk factor*

Introduction

International travellers are exposed to the acquisition of potential pathogens including viruses, bacteria or parasites with the risk of community or hospital spread upon return, whether or not they present health problems during their trip. Therefore, there is a risk of pathogens being imported into France from endemic areas abroad, either from foreign travellers visiting France, from French travellers visiting foreign countries, or via migrants and expatriates treated in France with a risk of indigenous spread. This has been extensively described, by example, among French Hajj pilgrims travelling to Mecca, Saudi Arabia [1].

An Australian organisation, Work the World, has enabled 15,000 medical students to take part in internships abroad since 2005 [2]. Developing countries are becoming popular destinations of internship. Medical internships abroad are generally hospital immersion experiences but, young medical students also participate in humanitarian missions that are unrelated to clinical activities such as school renovation for example [3, 4]. In one Australian survey, 64% of students experienced some sort of health problems while taking part in electives abroad, and travellers' diarrhoea was the most common problem (40%) [5]. In our preliminary report on a cohort of 134 French medical students participating in international electives, we showed that 73.9%, 38.8% and 5% of them reported gastrointestinal, respiratory, and vaginal symptoms, respectively [4]. We showed that the acquisition rate of Enteropathogenic *Escherichia coli* (EPEC) and Enteroaggregative *E. coli* (EAEC) was 41% and 53%, respectively. By contrast, the acquisition of respiratory viruses was low but was associated with persistent respiratory symptoms at return. Respiratory bacterial acquisition ranged from 3.3% for *Streptococcus pyogenes* to 15.0% for *Haemophilus influenzae*. *Atopobium vaginae* and *Gardnerella vaginalis* percentage of acquisition were 14.3% and 7.7%, respectively. So far, to our knowledge, the risk factors for acquisition of pathogens have not been clearly identified among medical students abroad to date. The relationship between symptoms and the carriage of pathogens

also remain poorly understood, making it difficult to distinguish between infection and colonisation. We aim to conduct this study to investigate the risk factors for symptoms of infections among French medical students undertaking an internship abroad.

Materials and methods

Study design

A monocentric prospective cohort survey was conducted over two years (2018–2019) among medical students from the Faculty of Medicine in Marseille, France who were planning to take part in an internship abroad during the summer. Recruitment was performed on a voluntary basis, during their vaccination and pre-travel consultation at the Institut Méditerranée Infection which is on the Marseille University medical campus. Participants were asked to complete an inclusion questionnaire including demographic data, history of chronic illness, intended travel dates and destination. All participants received advice regarding the prevention of diarrhoea during travel (hand hygiene, safe food, and water habits) but prophylaxis for traveller's diarrhoea was not prescribed. Because dates of departure and return are different for each student, the samples were not taken at once. The participants were given two sets of "pre-travel" and "post-travel" kits which contained questionnaire and sampling equipment (commercial rigid cotton-tipped swab applicators and viral transport media). They were also instructed how to self-collect samples, as following: 3 cm in the nostril, 5 turns and post wall of the pharynx, 5 streaks for respiratory samples; rectal samples were collected using two methods: rectal self-sampling when having a bowel movement, 3 centimetres through the anus, gently rubbing the inner walls of the rectum several times or stool collection after emission; vaginal samples were collected by placing the swab about three centimetres in the vagina and gently rubbing the inner walls several times, avoid touching the skin

and vulva with the swab. Samples were self-collected using commercial rigid cotton-tipped swab applicators (Medical Wire & Equipment, Wiltshire, UK) and placed in viral transport media (Sigma Virocul®) for further process at our laboratory. A document of instructions for self-sampling was also provided in the kits. During the week before travel, each student was invited to deposit their self-collect samples and a pre-travel questionnaire that collected information about their health problems and antibiotic use if applicable. After their travel, they were invited to self-collect samples during the week following their return to France. Students were also provided with a post-travel questionnaire addressing the exact place of the internship, the type of activities during their stay, including tourism and travel to other countries over the internship period. Accommodation conditions, contact with animals or children, symptoms, onset of symptoms and treatment during their stay were also documented. Influenza-like illness (ILI) was defined as sore throat, cough plus subjective fever [6]. Diarrhoea was defined by at least three loose or liquid stools per 24 hours.

Microbiological methods

The methods for identifying respiratory, gastro-intestinal, and vaginal pathogens by PCR assay are detailed elsewhere [4]. The followed respiratory pathogens were screened: Influenza A and B viruses, Human coronaviruses, Human parainfluenza viruses, Human rhinovirus, Human metapneumovirus, Adenovirus, Respiratory syncytial virus, *Staphylococcus aureus, H. influenzae*, *Streptococcus pneumoniae, Klebsiella pneumoniae*, and *S. pyogenes.* The following gastro-intestinal pathogens were screened for: Norovirus, Rotavirus, Adenovirus, Astrovirus, *Entamoeba histolytica*, *Giardia lamblia*, *Cryptosporidium* spp, *Salmonella* spp, *Shigella* spp (EIEC), Enterohemorrhagic *E. coli* (EHEC), Enteropathogenic *E. coli* (EPEC), Enteroaggregative *E. coli* (EAEC)*, Campylobacter jejuni* and *Tropheryma whipplei*. The following vaginal pathogens were screened for: *Chlamydia trachomatis*, *Mycoplasma genitalium, Neisseria gonorrhoeae, Trichomonas vaginalis, Mycoplasma hominis, A. vaginae* and *G. vaginalis.*

PCR were considered positive for virus or bacteria detection when the cycle threshold (CT) value was ≤35. Bacterial vaginosis was defined by a *G. vaginalis* DNA load ≥ 10^9 copies/mL (CT≤ 18) and/or an *A. vaginae* DNA load ≥ 10^8 copies/mL (CT≤ 21), as previously reported [7].

The acquisition of a pathogen was defined as negative before travel and positive when returning to Marseille, France.

Statistical analysis

STATA software version 14.2 was used to conduct statistical analysis. Differences in the proportions were tested by using Fisher's exact or Pearson's chi-square tests, when appropriate. McNemar's test was used to evaluate the potential acquisition of pathogens (prevalence after versus before travel). Clinical symptoms during travel were reported only if onset of symptoms took place during travel. Univariate analysis was used to evaluate unadjusted associations between the prevalence of symptoms during travel and multiple factors. A p-value <0.05 was considered to be statistically significant. Only variables with a prevalence equal or more than 5.0% were considered for statistical analysis. Variables with p-values <0.2 in the univariate analysis were included in the multivariate analysis. Log-binomial regression was used to estimate factors' adjusted risk ratios for symptoms of infections.

Ethics

The protocol was approved by our Institutional Review Board (2019-006). It was performed in accordance with the good clinical practices recommended by the Declaration of Helsinki and its amendments. All participants gave their written informed consent.

Results

Characteristics of study participants

A total of 293 students agreed to participate and answered the post-travel questionnaire. The M/F gender ratio was 0.31 with a median age of 21 years (ranging from 18 to 25 years). Most participants (80.9%) were students in their second year of medical studies and were taking part in a non-medical humanitarian mission. The remaining participants were in their 4th year of study and were assigned to different departments of medicine or surgery for clinical training (Supplementary Table S1).

The primary travel destinations for internships were in Africa (29.0%), South East Asia (27.7%), South America (21.8%) and South Asia (18.8%). The top five primary destination countries were Vietnam (24.2%), India (18.8%), Peru (16.4%), Tanzania (10.2%) and Madagascar (9.2%). The mean travel duration was 41 days ± 11.1 days (ranging from 16 to 78 days). Accommodation conditions were judged as being "very clean" by 14.7% (43/293) of students, "clean" by 44% (129/293) and "very basic" by 41.3% (121/293). 42.7% and 79.9% of the participants reported contact with animals and local children, respectively (Supplementary Table S2). During their stays, 94.2% also travelled as tourists in the country of primary destination and 50 (17.1%) visited other countries. The top five additional destination countries were Laos (4.8%), Cambodia (4.4%), Bolivia (3.4%), Thailand (1.7%) and Argentina (1.7%).

A total of 55/293 (18.8%) were vaccinated against influenza and only 2/293 (0.7%) against invasive pneumococcal infections at inclusion. In addition, 260/293 (88.7%) and 273/ 293 (93.2%) student were vaccinated against hepatitis A and hepatitis B before travel, respectively.

Overall, 5.1% took antibiotics in the week before departure and 17.8% took doxycycline as a chemoprophylaxis against malaria during their stay.

Respiratory infections

159 A total of 35.8% (105/293) students reported respiratory symptoms during travel. The median time
160 between arrival at the travel destination and the onset of symptoms was 17 days [ranging from 1 to
161 58 days]. The most frequent respiratory symptoms were rhinitis (27.1%), sore throat (21.8%) and
162 cough (20.1%), followed by fever (9.6%) and dyspnoea (6.5%) (Figure 1a). 7.9% of students
163 declared persistence of symptoms on their return to France and 5.5% took antibiotics (ATB) for
164 respiratory symptoms during travel.

165 A total of 275 (93.9%) students provided paired nasopharyngeal swabs. 52.4% of students acquired
166 at least one respiratory pathogen. 17.8% of (49/275) students acquired at least one respiratory virus
167 with human rhinovirus (14.6%) being the most frequent. Twenty-three students were still
168 symptomatic after returning to France. Of whom, 16 (69.6%) were positive for at least one
169 pathogens. Bacterial acquisition rates were higher (40.7%), with *S. aureus* (18.9%) being the most
170 frequent, followed by *H. influenza* (17.1%) (Table 1). A total of 6.2% students acquired a virus-
171 bacteria combination and 11.6% a bacteria combination. When comparing the post- versus pre-
172 travel prevalence of pathogens, a significant increase was observed for rhinovirus and *S.*
173 *pneumoniae*.

174 ***Gastro-intestinal infections***

175 A proportion of 63.5% of students reported at least one gastro-intestinal symptom, all during travel
176 and only one following return. The median time between arrival at the travel destination and the
177 onset of symptoms was 13 days [ranging from 1 to 65 days]. The most frequent symptoms were
178 diarrhoea (48.1%) and abdominal pain (46.4%), followed by nausea (26.3%) and constipation
179 (19.8%) (Figure 1b). 8.9% reported persistent symptoms on return to France and 3.4% took an
180 antibiotic for diarrhoea during their stay.

A total of 274 (93.5%) students provided paired rectal swabs. Three students reported gastrointestinal symptoms at day 1 after departure. But all rectal samples pre-travel were negative for gastrointestinal pathogens. 51.5% students acquired at least one gastrointestinal pathogen. Nine students (3.3%) acquired at least one virus (adenovirus, astrovirus and norovirus). Bacterial acquisition rates were higher (49.3%), notably for EAEC (40.9%) and EPEC (18.6%). Additionally, 2.6% of individuals acquired *Shigella* spp/EIEC, 1.5% *Salmonella* spp and 1.1% *G. lamblia* (Table 2). When comparing the post- versus pre-travel prevalence of pathogens, a significant increase was observed for viruses overall, EAEC, EPEC, *Salmonella* spp and *Shigella* spp/EIEC.

Vaginal infections

Of the 224 female students, eight (3.6%) reported vaginal symptoms such as leucorrhoea, during their stay, and two took antibiotics for this purpose. The median time between arrival at the travel destination and the onset of symptoms was 26 days [ranging from 6 to 59 days]. Three students (1.3%) were still symptomatic on returning to France.

209 (93.3%) of the participants provided paired vaginal samples. 15.8% of the participants acquired at least one vaginal microorganism with the highest acquisition rate for *A. vaginae* (13.9%) and *G. vaginalis* (12.9%) (Table 3). Nine students (4.0%) had molecular criteria for bacterial vaginosis on return. When comparing the post- versus pre-travel prevalence of microorganisms, a significant increase was observed for *G. vaginalis* (CT<18), indicative of vaginosis.

Risk factors for symptoms of infections

Being female, primarily travelling to Vietnam, and living in basic accommodation conditions were independent risk factors for reporting respiratory symptoms. Students suffering respiratory symptoms were 3 times more likely to acquire *S. pneumoniae* during travel. Travelling primarily to north India and Senegal were independent risk factors for reporting diarrhoea (Table 4).

Discussion

Most students in our study travelled to low-income tropical countries for about two months and participated in humanitarian missions in relatively basic conditions of housing and in close contact with local children and animals. Two-thirds of students reported gastrointestinal symptoms (notably diarrhoea, abdominal pain and nausea-vomiting which are suggestive of gastroenteritis) and one-third of students reported respiratory symptoms (notably rhinitis, a sore throat and a cough which are suggestive of an upper respiratory tract infection). These symptoms appeared within 2 weeks of their arrival at destination of their internship. Moreover, we observed a low proportion of travel-associated vaginal symptoms. Overall, symptoms were relatively mild with fewer than 5% students requiring antibiotics and most symptoms resolved before students came back to France. This result is consistent with other studies realized on medical students abroad, confirming the fact that despite reinforced pre-travel counselling, travel-associated respiratory infections and travellers' diarrhoea were very frequent among medical students who were fully aware of the ways to prevent these illnesses [5, 8-10].

We found a significant acquisition of human rhinovirus and *S. pneumoniae* as reported previously among international travel as well as among Hajj pilgrims [1, 11, 12]. We also observed a high acquisition rate of EAEC (40.9%) and EPEC (18.6%) among health students, as documented in other studies realized in different populations of domestic and international travellers [13-18].

Our results showed that respiratory symptoms were significantly more frequent in female. We have no explanation for this observation. Interestingly, the travel destination was distinctly associated with symptoms. Travel to India and Senegal was a risk factor for diarrhoea while travel to Vietnam was a risk factor for respiratory symptoms. Our results are discordant with those of a previous study

on 649 international travellers showing that respiratory infections (sore throat or cough) were significantly increased in travellers returning from the non-tropical regions (7.6%) than those from tropical regions, including Vietnam (2.0%) [19]. Differences by travel destination are also known to be relative to the incidence of travellers' diarrhoea. This result was in line with most other studies that have also found that travelling to the Indian subcontinent was a highest relative risk for diarrhoea, followed by African regions [16, 20-23].

In addition, the observed correlation between respiratory symptoms and very basic accommodation conditions suggests that precarious housing conditions may encourage respiratory infections. A significant association between the acquisition of *S. pneumoniae* and respiratory symptoms was also observed in cohorts of Hajj pilgrims [24].

We observed no significant association between *E. coli* acquisition and diarrhoea in our study, in contrast to other studies where EAEC or EPEC have been reported to be more frequent in travellers with diarrhoea returning from several geographical areas [14, 16, 25]. This may be explained by the onset of gastro-intestinal symptoms occurring early during the trip, while sampling was performed on return, several weeks later. Furthermore, asymptomatic carriage of potential pathogens was also observed in participants. In a study by Adachi *et al.,* EAEC was detected in the stools of 26% of patients with traveller's diarrhoea returning from Mexico, Jamaica, or India [26]. On the other hand, a recent case-controlled study conducted on German and Dutch travellers showed that EAEC detection was not significantly different in diarrheal persons and asymptomatic controls. However, the prevalence of this bacterium among participants suffering from diarrhoea during international travel was high (40.0%) [14]. Such results are in line with ours.

Our study has a few limitations. First, this study was monocentric and conducted on a very specific population of travellers which impairs generalisation of our findings. Also, qPCR does not

differentiate between dead and viable microorganisms. Finally, sampling was realized during the week preceding departure and during the week following return, samples at onset of symptoms were not available. Among students who reported clinical symptoms early after their arrival abroad, we are not sure whether these students were infected before or after departure, since incubation times of diseases are very different and may vary (Supplementary table S3). Likewise, post-travel samples were collected at a significant time after the onset of symptoms during travel and responsible pathogens may have been partly cleared.

This study makes it possible to identify the main infectious diseases linked to travel in a group of French medical students undertaking an internship abroad and risk factors upon which to base targeting students for reinforced pre-travel advice. Sampling at the time of the onset of symptoms should be carried out in future studies to better understand the relationship between the carriage of pathogens and symptoms.

Transparency declaration

The authors declare that there are no conflicts of interest.

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Table 1: Prevalence of respiratory pathogens

Variables	Pre-travel		Post-travel		Acquisition		p*
	n = 275[1]	%	n = 279[2]	%	n =275[3]	%	
Viruses							
Adenovirus	1	0.4	0	0	0	0	NA
Coronaviruses	1	0.4	6	2.2	6	2.2	0.06
Coronavirus HKU1	0	0	3	1.1	3	1.1	0.08
Coronavirus 229E	0	0	2	0.7	2	0.7	0.16
Coronavirus NL63	1	0.4	1	0.4	1	0.4	1.0
Coronavirus OC43	0	0	0	0	0	0	NA
Influenza A	0	0	1	0.4	1	0.4	0.32
Influenza B	0	0	2	0.7	2	0.7	0.16
Metapneumovirus	0	0	0	0	0	0	NA
Parainfluenza virus	0	0	0	0	0	0	NA
Respiratory syncytial virus	1	0.4	2	0.7	2	0.7	0.56
Rhinovirus	25	9.1	44	15.8	40	14.6	0.015
At least one virus	26	9.5	54	19.6	49	17.8	0.001
Bacteria							
Haemophilus influenzae	122	44.4	119	42.7	47	17.1	0.76
Klebsiella pneumoniae	23	8.4	28	10.0	19	6.9	0.38
Staphylococcus aureus	63	22.9	83	29.8	52	18.9	0.052
Streptococcus pneumoniae	5	1.8	15	5.4	15	5.5	0.025
Streptococcus pyogenes	3	1.1	8	2.9	7	2.6	0.096
At least one bacteria	161	58.6	180	64.5	112	40.7	0.11
Virus and bacteria combination	13	4.7	29	10.4	17	6.2	0.01
H. *influenzae*-rhinovirus	9	3.3	13	4.7	4	1.5	0.37
K. *pneumoniae*-rhinovirus	1	0.4	1	0.4	0	0	NA

S. *pneumoniae*-rhinovirus	0	0	1	0.4	1	0.4	0.32
S. *aureus*-rhinovirus	6	2.2	12	4.3	8	2.9	0.16
Bacteria combination of two bacteria	61	22.2	87	31.2	32	11.6	<0.000
H. *influenza* - K. *pneumoniae*	12	4.4	15	5.4	3	1.1	0.49
H. *influenza* - S. *pneumoniae*	4	1.5	11	3.9	5	1.8	0.07
H. *influenza* - S. *aureus*	36	13.1	40	14.3	12	4.4	0.55
H. *influenzae*-S. *pyogenes*	3	1.1	5	1.8	1	0.4	0.41
K .*pneumoniae*-S. *pneumoniae*	0	0	3	1.1	3	1.1	0.08
K. *pneumoniae*-S. *aureus*	4	1.5	7	2.5	2	0.7	0.26
K. *pneumoniae*-S. *pyogenes*	0	0	0	0	0	0	NA
S. *pneumoniae*-S. *aureus*	1	0.4	6	2.1	6	2.2	0.06
S. *pneumoniae*-S. *pyogenes*	0	0	0	0	0	0	NA
S. *aureus*-S. *pyogenes*	1	0.4	0	0	0	0	NA
At least one pathogen	174	63.3	205	73.5	144	52.4	0.008

* p-value: pre- versus post-travel, McNemar's test

1, 2: 275 and 279 students provided pre- and post-travel nasopharyngeal swabs, respectively

3: Acquisition of respiratory pathogens was calculated in 275 students who provided both pre- and post-travel nasopharyngeal samples

Table 2: Prevalence of gastrointestinal pathogens

Pathogens	Pre-travel		Post-Travel		Acquisition		p*
	N = 282[1]	%	N = 283[2]	%	N = 274[3]	%	
Viruses							
Adenovirus	0	0	3	1.1	3	1.1	0.08
Astrovirus	0	0	3	1.1	3	1.1	0.08
Norovirus	0	0	3	1.1	3	1.1	0.08
Rotavirus	0	0	0	0	0	0	NA
At least one virus	0	0	9	3.2	9	3.3	0.003
Bacteria							
Campylobacter jejuni	2	0.7	5	1.8	5	1.8	0.26
Enteroaggregative *Escherichia coli*	10	3.6	119	42.1	112	40.9	< 0.000
Enterohemorrhagic *E. coli*	3	1.1	4	1.4	2	0.7	0.65
Enteropathogenic *E. coli*	25	8.9	66	23.3	51	18.6	< 0.000
Salmonella spp	0	0	4	1.4	4	1.5	0.05
Shigella spp/EIEC	0	0	7	2.5	7	2.6	0.008
Tropheryma whipplei	1	0.4	1	0.4	0	0	NA
At least one bacteria	38	13.5	147	51.9	135	49.3	< 0.000
Parasites							
Cryptosporidium parvum/hominis	0	0	0	0	0	0	NA
Entamoeba histolytica	0	0	0	0	0	0	NA
Giardia lamblia	1	0.4	3	1.1	3	1.1	0.32
At least one gastrointestinal pathogen	39	13.8	153	54.1	143	52.2	< 0.000

* p-value: pre- versus post- travel, McNemar's test

1, 2: 282 and 283 students provided pre- and post-travel rectal swabs, respectively

3: Acquisition of gastrointestinal pathogens was calculated in 274 students who provided both pre- and post-travel rectal samples

Table 3: Prevalence of vaginal microorganisms

Microorganisms	Pre-travel N =212[1] (%)	Post-travel N= 221[2] (%)	Acquisition N = 209[3] (%)	p *
Bacteria				
Atopobium vaginae	42 (19.8)	42 (19.0)	29 (13.9)	0.896
Atopobium vaginae (CT<21)	1 (0.5)	1 (0.5)	1 (0.5)	1.0
Chlamydia trachomatis	1 (0.5)	1 (0.5)	1 (0.5)	1.0
Gardnerella vaginalis	59 (27.8)	55 (24.9)	27 (12.9)	0.439
Gardnerella vaginalis (CT<18*)*	2 (0.9)	9 (4.1)	9 (4.3)	0.035
Mycoplasma genitalium	0	2 (0.9)	2 (0.96)	0.16
Mycoplasma hominis	4 (1.9)	3 (1.4)	2 (0.96)	0.65
Neisseria gonorrhoeae	0	0	0	NA
Parasites				
Trichomonas vaginalis	0	0	0	NA
At least one vaginal pathogen	82 (38.7)	78 (35.3)	33 (15.8)	0.42

* p-value: pre- versus post-travel, McNemar's test

1, 2: 212 and 221 students provided pre- and post-travel vaginal swabs, respectively

3: Acquisition of vaginal pathogens was calculated in 209 students who provided both pre- and post-travel vaginal samples

Table 4: Risk factors for respiratory symptoms and diarrhoea during travel

	Risk factors for respiratory symptoms during the travel					Risk factor for diarrhoea during the travel				
	Univariate analyse				**Multivariate analyse**	**Univariate analyse**				**Multivariate analyse**
	No n (%)	Yes n (%)	RR [95%CI]	p	aRR [95%CI], p	No n (%)	Yes n (%)	RR [95%CI]	p	aRR [95%CI], p
Gender										
Female	136 (72.3)	88 (83.8)	1.50 [1.06-2.11]	0.02	1.55 [1.08-2.22], p= 0.02	121 (54.0)	103 (46.0)	0.77 [0.51-1.15]	0.19	-
Male	52 (27.7)	17 (16.2)				31 (44.9)	38 (55.1)			
Age (mean ± SD)	20.7±1.1	20.7±1.1	t= 0.38 0.70	0.70		20.7 ± 1.1	20.6± 1.1	t=0.70	0.48	
Medical history										
Vaccination against influenza	83 (34.9)	22 (40.0)	1.15 [0.78-1.70] 0.48	0.48		NA	NA	NA	NA	
Primary travel destination										
South East Asia	71 (33.5)	34 (42.0)	1.26 [0.89-1.77]	0.18	-	104 (49.1)	37 (45.7)	0.93 [0.71-1.22]	0.61	

Vietnam	73 (32.9)	32 (45.1)	1.40 [0.97-2.00]	0.07	1.57 [1.07-2.31], p= 0.02	111 (50.0)	30 (42.3)	0.85 [0.62-1.14]	0.26	
South Asia	86 (36.1)	19 (34.6)	0.96 [0.65-1.40]	0.82		107 (45.0)	34 (61.8)	1.38 [1.07-1.77]	0.02	-
South India	98 (37.4)	7 (22.6)	0.66 [0.41-1.05]	0.08	-	125 (47.7)	16 (51.6)	1.08 [0.75-1.56]	0.68	
North India	93 (34.6)	12 (50.0)	1.53 [0.84-2.79]	0.16	-	123 (45.7)	18 (75.0)	1.64 [1.26-2.14]	<0.01	2.57 [1.13-5.85] p= 0.025
Africa	77 (37.0)	28 (32.9)	0.89 [0.65-1.24]	0.51		105 (50.5)	36 (42.4)	0.84 [0.63-1.11]	0.21	
Tanzania	99 (37.6)	6 (20.0)	0.61 [0.38-0.97]	0.04	-	137 (52.1)	4 (13.3)	0.26 [0.10-0.64]	<0.000	0.37 [0.22-0.60] p <0.000
Madagascar	91 (34.2)	14 (51.9)	1.63 [0.92-2.90]	0.09	-	129 (48.5)	12 (44.4)	0.92 [0.59-1.42]	0.69	
Senegal	98 (35.3)	7 (46.7)	1.37 [0.82-2.83]	0.40		129 (46.4)	12 (80.0)	1.72 [1.30-2.29]]	0.01	3.31 [1.05-10.45] p= 0.04
South America	84	21	0.90	0.569		108	33	1.09	0.53	

	(36.7)	(32.8)	[0.63-1.29]			(47.2)	(51.6)	[0.83-1.44]	
Peru	87 (35.5)	18 (37.5)	1.06 [0.70-1.58]	0.79		114 (46.5)	27 (56.3)	1.21 [0.91-1.60]	0.22
Condition during travel									
Contact with children	18 (30.5)	87 (37.2)	1.20 [0.83-1.73]	0.33		27 (45.8)	114 (48.7)	1.06 [0.78-1.45]	0.69
Contact with animals	52 (31.0)	53 (42.4)	1.37 [1.01-1.86]	0.046	-	77 (45.8)	64 (51.2)	1.12 [0.88-1.42]	0.36
Type of accommodation									
Very clean	34 (79.1)	9 (20.9)	rfr	rfr	rfr	22 (51.2)	21 (48.8)	rfr	Rfr
Clean	84 (65.1)	45 (34.9)	1.49 [0.96-2.29]	0.07	-	73 (56.6)	56 (43.4)	0.86 [0.53-1.40]	0.54
Basic	70 (57.9)	51 (42.2)	1.81 [1.16-2.82]	<0.01	1.43 [1.02-1.99], p= 0.04	57 (47.1)	64 (52.9)	1.13 [0.68-1.86]	0.65
Mission during travel									
Humanitarian mission in an orphanage	94 (39.2)	11 (20.8)	0.60 [0.41-0.87]	<0.01	-	115 (47.9)	26 (49.1)	1.02 [0.76-1.39]	0.88

School renovation	49 (31.4)	56 (40.9)	1.29 [0.96-1.75]	0.09	-	79 (50.6)	62 (45.3)	0.89 [0.70-1.14]	0.36	
Supply of medical equipment and health advice	86 (35.0)	19 (40.4)	1.16 [0.77-1.76]	0.48		117 (47.6)	24 (51.1)	1.07 [0.79-1.46]	0.66	
Internships in hospital	86 (36.3)	19 (33.9)	0.94 [0.64-1.37]	0.74		112 (47.3)	29 (51.8)	1.10 [0.82-1.46]	0.54	
Internships in surgery department	97 (35.3)	8 (44.4)	1.29 [0.82-1.12]	0.45		130 (47.3)	11 (61.1)	1.29 [0.88-1.91]	0.26	
Duration of travel (mean ± SD)	40.5 ±10.7	41.8 ±11.9	t=-0.95	0.34		39.6± 10.7	42.6± 11.4	t=-2.35	0.02	-
Acquisition of respiratory pathogens[275]										
Rhinovirus	86 (36.6)	11 (27.5)	0.78 [0.51-1.19]	0.25		NA	NA	NA	NA	
At least one respiratory virus	84 (37.2)	13 (26.5)	0.75 [0.50-1.10]	0.14	-	NA	NA	NA	NA	
Haemophilus influenzae	79 (34.7)	18 (38.3)	1.10 [0.73-1.67]	0.64		NA	NA	NA	NA	
Klebsiella pneumoniae	89 (34.8)	8 (42.1)	1.22 [0.65-2.29]	0.53		NA	NA	NA	NA	

Staphylococcus aureus	78 (35.0)	19 (36.5)	1.04 [0.70-1.55]	0.83		NA	NA	NA	NA
Streptococcus pneumoniae	87 (33.5)	10 (66.7)	2.70 [1.10-6.62]	0.03	2.79 [1.13-6.88], p= 0.03	NA	NA	NA	NA
At least one respiratory bacteria	56 (34.4)	41 (36.6)	1.06 [0.78-1.45]	0.70		NA	NA	NA	NA
Acquisition of digestive pathogens[274]									
Enteroaggregative *Escherichia coli*	NA	NA	NA	NA		78 (48.2)	58 (51.8)	1.08 [0.85-1.37]	0.55
Enteropathogenic *E. coli*	NA	NA	NA	NA		110 (49.3)	26 (51.0)	1.03 [0.77-1.40]	0.83
At least one gastrointestinal bacteria	NA	NA	NA	NA		68 (48.9)	68 (50.4)	1.04 [0.74-1.47]	0.81
At least one gastrointestinal pathogen	NA	NA	NA	NA		64 (48.9)	72 (50.4)	1.04 [0.74-1.47]	0.81

NA: not applicable

RR: relative risk, aRR: adjusted relative risk, CI: confidence interval, p: p value, rfr: reference

¥ Number of individuals for whom data were available

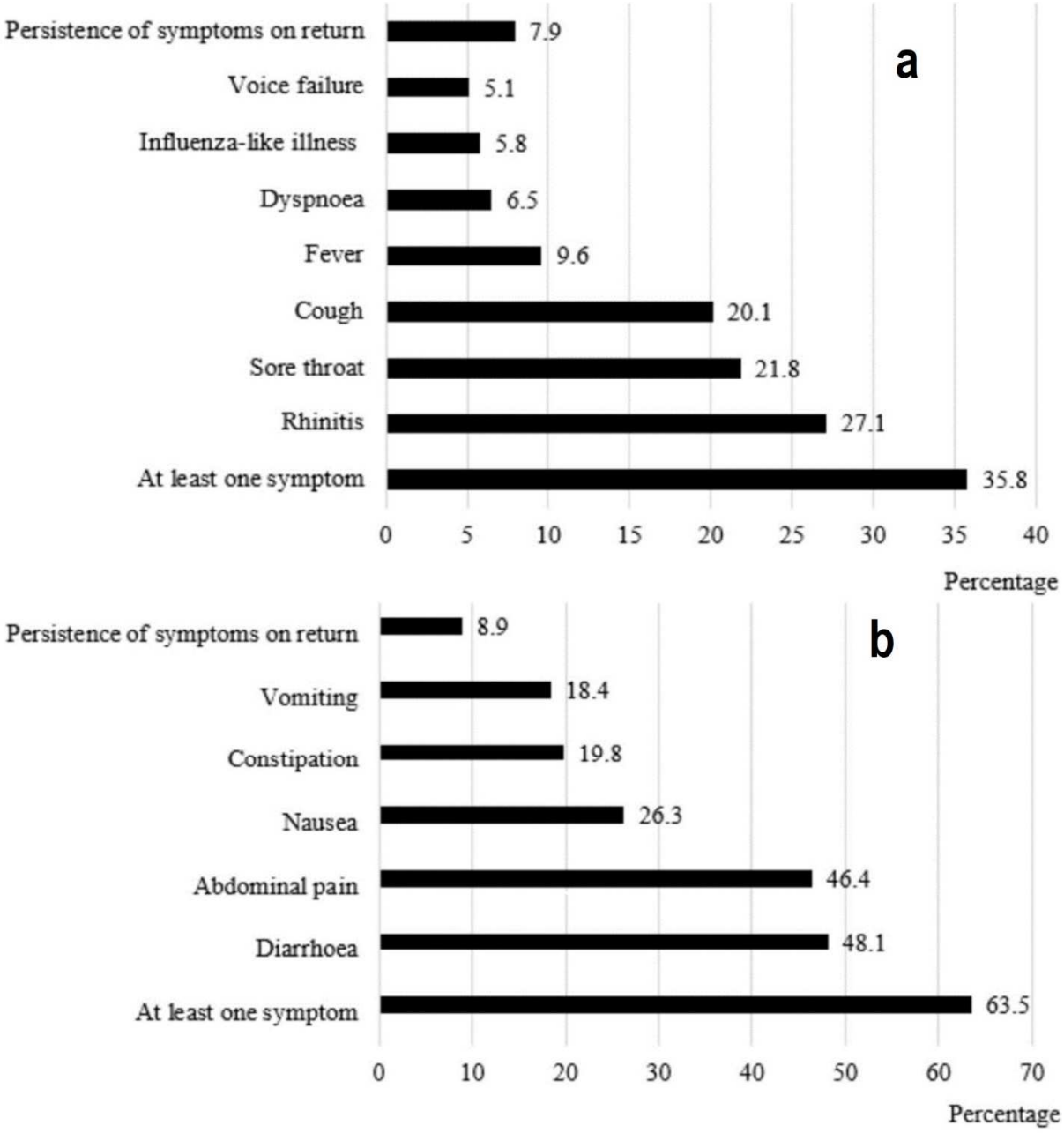

Figure 1: Prevalence of respiratory **(a)** and gastrointestinal **(b)** symptoms during travel